Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 9-16 and 21 are pending in the application, with claim 9 being the sole independent claim. Claim 16 has been amended in order to more clearly and precisely define the subject matter of the claimed invention. Support for the amendment can be found, for example, in the specification at page 5, lines 10-11. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Reply to the Restriction Requirement with Traverse

In reply to the restriction requirement made by the Examiner, requesting an election of one invention to prosecute in the above-referenced patent application, Applicants hereby provisionally elect to prosecute the invention of Group I, represented by claims 9-16 and 21. This election is made without prejudice to or disclaimer of the other claims or inventions disclosed.

This election is made ***with*** traverse.

The Examiner has requested election of claims 9-16 and 21 (Group I), drawn to a nucleic acid construct encoding a protein (normally not secreted from a cell) fused to a signal peptide, wherein the 3'-UTR of the protein is altered relative to the naturally occurring RNA encoding the protein, such that the 3'-UTR effect on directing the protein to an intracellular location other than the endoplasmic reticulum is eliminated or reduced. As the

Examiner notes, these claims are also drawn to vectors, host cells, proteins, chimeric proteins and methods of making proteins. In the alternative, the Examiner has requested election of claims 9 and 15 (Group II), drawn to the nucleic acid as described above and a mammalian cell comprising said nucleic acid, wherein the mammalian cell is in a cell culture or in a non-human animal.

Applicants respectfully traverse the restriction requirement as it applies to Groups I and II. The Examiner alleges that Groups I and II are patentably distinct inventions. However, even where patentably distinct inventions appear in a single application, restriction remains improper unless the examiner can show that the search and examination of the groups would entail a "serious burden" (*see* MPEP § 803.) In the present situation, the examiner has failed to make such a showing.

Applicants assert that a search and examination of the subject matter of Groups I and II would not entail a serious burden. Specifically, a separate search of the subject matter of claim 15 is unnecessary if claim 9, from which claim 15 depends, is found to be novel and unobvious. This is the case because if the nucleic acid of claim 9 is found to be novel and unobvious, then by definition, a mammalian cell comprising the nucleic acid of claim 9 would be novel and unobvious because claim 9 is not limited by the presence of the nucleic acid in a particular cell type. Accordingly, a search of Group II would not entail a serious burden on the Examiner, once a search for Group I has been completed.

In view of the above, reconsideration and withdrawal of the Restriction Requirement, and consideration and allowance of all pending claims, are respectfully requested.

Rejections under 35 U.S.C. § 112

The Examiner has rejected claim 16 under 35 U.S.C. § 112, second paragraph, for allegedly being "incomplete." (Paper No. 11, page 4.) Solely to advance prosecution and

not in acquiescence to the Examiner's rejection, the Applicants have amended claim 16 in accordance with the Examiner's suggestion. Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 9-16 under 35 U.S.C. § 103(a) as allegedly unpatentable over Lee *et al.* (IDS Document No. AT5) in view of Kordula *et al.*, *Biochem J. 293:* 187-93 (1993) and further in view of Maeda *et al.* (IDS Document No. AS6). Applicants respectfully disagree with the Examiner.

The Examiner suggests that one of ordinary skill in the art, looking to produce secreted proteins which are normally not secreted by a cell, would combine the disclosure of Lee *et al.* (i.e., that a protein normally expressed as a membrane-bound protein (sialytransferase) can be secreted from a cell by adding a mammalian signal peptide), with the disclosure of Kordula *et al.* (i.e., a nucleic acid sequence encoding a mammalian protein which sequence has a disrupted 3'-UTR).

The Examiner appears to consider that the teaching of Kordula *et al.* would motivate the skilled person to modify the vector of Lee *et al.* Applicants submit that this assertion is incorrect because there is no motivation to modify the nucleic acid of Lee *et al.* As pointed out in Applicants' previous response, the nucleic acid of Lee *et al.* is naturally directed to the endoplasmic reticulum. Thus, the 3'-UTR of this nucleic acid does not try to direct it to other parts of the cell.

The Examiner also states that one of ordinary skill in the art would have been motivated to combine these references "in order to be able to produce secreted proteins which are not normally secreted by a cell in order to obtain larger quantities of the protein for purification and potential medical use." (Paper No. 11, pages 5-6.) A determination of

obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to *particular* sources of information, to select *particular* elements, and to combine them in the way they were combined by the inventor. *ATD Corp v. Lydall, Inc.*, 159 F.3d 534 (Fed. Cir. 1998). Applicants submit that the Examiner's asserted motivation to combine is nothing more than a generalized desire in the art, lacking any particularity. Thus, contrary to the Examiner's assertion, there is no motivation to combine Lee *et al.* and Kordula *et al.* "A general incentive does not make a particular result obvious, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995).

Assuming, *arguendo*, that one of ordinary skill in the art were motivated to combine the Lee *et al.* and Kordula *et al.* references, there is nothing in Kordula *et al.* that would suggest that the 3'-UTR thereof should be modified or could be modified with any reasonable likelihood of success. Kordula *et al.* is concerned with expression in a *prokaryotic* system, whereas the present invention is concerned with expression in a *eukaryotic* system. Thus, in Kordula *et al.*, the signals in the nucleic acid which are involved with targeting within a eukaryotic cell are completely irrelevant.

More specifically, Kordula *et al.* describe the work where the coding region (i.e., with a "disrupted" 3' UTR) of the horse elastase inhibitor (HLEI) was cloned into the bacterial expression vector pKK233-2 expressed in *E. coli* cells. Following expression of the full length coding region for HLEI in *E. Coli* cells, Kordula *et al.* sonicated the harvested product in order to release the protein (page 188, para. 3). HLEI was then detected by electrophoresis/Western blotting. The protein was detected in the soluble cell fraction as well as in inclusion bodies (page 191). The protein was not secreted from the bacteria.

Since the 3'-UTR had been removed, it is impossible to conclude any possible effects this may have had on targeting of the mRNA. Furthermore, *E. Coli* is naturally devoid of a mammalian ER membrane system making any form of comparison concerning the biological importance of the 3'-UTR absolutely futile.

Moreover, the use of a NcoI-HindIII fragment of the coding region of HLEI in a bacterial expression vector is in accordance with normal practice using prokaryotic expression systems. However, because of the large differences between expression in bacterial systems and eukaryotic systems (e.g., bacterial mRNAs do not contain 3'-UTRs and bacteria do not have an ER-based secretion system), the findings Kordula *et al.* do not teach anything about requirements for expression in mammalian cells.

In view of the above, Applicants assert that, contrary to the Examiner's assertion, one of ordinary skill in the art would not be motivated to combine the teachings of the cited references because of the great differences in bacterial protein expression (Kordula *et al.*) and mammalian protein expression (Lee et *al.*). These differences would also make it unlikely that one skilled in the art would combine the references with a reasonable expectation of success. Thus, the cited references do not render Applicants' claimed invention unpatentable. Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has also rejected claim 13 under the additional reference of Maeda *et al.* As discussed above, there is no motivation to combine Lee *et al.* and Kordula *et al.* Maeda *et al.* fail to cure the defects of Lee *et al.* and Kordula *et al.* Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner has also rejected claim 21 under 35 U.S.C. § 103(a) as allegedly being unpatenable over Lee *et al.* in view of Kordula *et al.* and further view of Smith and Johnson, *Gene 67*:31-40 (1988). As discussed above, there is no motivation to combine Lee *et al.*

and Kordula *et al.* Smith and Johnson fail to cure the defects of Lee *et al.* and Kordula *et al.* Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

16. A method of obtaining a protein from a mammalian cell, comprising expressing the protein in the cell using [a]the nucleic acid of claim 9 [and], allowing the cell to secrete the protein and purifying the protein.